UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,134	07/11/2003	Gerold Schuler	106985-2 KGB	4429

27384 7590 07/01/2008

NORRIS, MCLAUGHLIN & MARCUS, PA
875 THIRD AVENUE
18TH FLOOR
NEW YORK, NY 10022

EXAMINER
JUEDES, AMY E

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
07/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,134	SCHULER ET AL.	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,11,29,30 and 35-38* is/are pending in the application.

4a) Of the above claim(s) *36 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,11,29,30,35 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of anti-CD3 and anti-CD28 as the species of activating the T cells, in the reply filed 4/24/08, is acknowledged.

Applicant's traversal is on the grounds that the amendment to the claims narrows the scope of the claims, and that there would be no burden to examine the amended claims since the original search would have necessarily covered the subject matter of the narrower amended claims. Applicant has amended claim 9 to recite that the T cells are "activated" T cells, and has further added new claims 37-38 reciting further method steps to produce activated T cells by stimulation with anti-CD3 and anti-CD28 antibodies, or by stimulation with mature dendritic cells. The previous claims did not require an activation step, and therefore, no search has been performed for the limitations of newly added claims 37-38, as asserted by Applicant. Furthermore, a search for stimulation with anti-CD3 and anti-CD28, or with dendritic cells requires consideration of distinct species of methods employing different reagents and method steps. It is a burden to search more than one invention. Applicant further argues that the restriction is improper coming at this late state of prosecution since the examiner should have anticipated the amendment to claim 9 to recited "activated" T cells since the specification discloses that the T cells need to be activated in order to anergize CD25- T cells. Applicant's amendment to the claims to recite patently distinct species of methods of activation has necessitated the restriction requirement. The examiner cannot be expected to anticipate and search for limitations not present in the claims, when in fact said limitations are not even disclosed by the specification (see new matter rejection below).

The requirement is still deemed proper and is therefore made FINAL.

Applicant indicates that claims 9, 11, 29-30, and 35-38 read on the elected invention. However, claim 36 recites that the T cells are contacted with activated T cells in vivo. Applicant's elected method involves activating T cells by subjecting the T cells to plate-bound anti-CD3 and anti-CD28 antibodies (i.e. an ex-vivo or in vitro method). Thus, claims 36 and 38 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected

invention.

Claims 9, 11, 29-30, 35, and 37 are being acted upon.

2. The rejection of the claims under 35 U.S.C. 102 as being anticipated by Baecher-Allan et al. is withdrawn in view of Applicant's amendment to the claims. Baecher-Allan et al. do not teach contacting CD4+CD25- T cells with CD4+CD25+ T cells that have been activated with plate bound anti-CD3 and soluble anti-CD28 antibodies.

3. In view of Applicant's amendment and restriction reply, the rejection of the claims under 35 U.S.C. 102 as being anticipated by Jonuleit et al. is withdrawn. Jonuleit et al. do not teach the elected species of activation (i.e. subjecting the cells to plate-bound anti-CD3 and soluble anti-CD28 antibodies). However, Applicant's arguments relevant to the new grounds of rejection will be addressed below.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 11, 29-30, and 35 stand rejected, and claim 37 is rejected, under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A method comprising "separating human Tr1-like regulatory cells from CD4+CD25+ T cells (Claim 9, and dependant claims 11, 29-30, and 35-36).

Applicant indicates that support for the new limitations of the claims can be found on page 3 and examples 4 and 5 of the specification, as well as in original claim 4.

A review of the specification fails to reveal support for the new limitations.

At page 3 the specification discloses obtaining Tr1-like regulatory T cells by

anergizing CD4+CD25- T cells by contact with CD4+CD25+ T cells. However, the specification does not disclose "separating" the Tr1-like regulatory cells "from CD4+CD25+ T cells. Original claim 4 is drawn to "isolated" Tr1-like regulatory T cells obtainable by anergizing CD4+CD25- T cells. However, "isolated" Tr1 like regulatory T cells does not have the same scope as regulatory T cells "separated" from CD4+CD25+ T cells. Moreover, original claim 4 is drawn to a regulatory T cell obtainable by anergizing a CD4+CD25- T cell, and not to a method of producing a regulatory T cell comprising anergizing CD4+CD25- T cells by contact with CD4+CD25+ T cells. Examples 4 and 5 of the specification describe specific examples in which CFSE labeled CD4+CD25- T cells are cultured at a particular ratio with CD4+CD25+ T cells, followed by FACS sorting the CFSE labeled and unlabelled cells. However, this specific example does not provide adequate support for the more generic method now claimed, which encompasses contacting cells at any ratio, followed by separating the cells by any means.

Applicant's arguments filed 1/7/08 have been fully considered, but they are not persuasive.

Applicant argues that the original claims disclose a method of producing isolated Tr1-like regulatory T cells by contacting CD4+CD25- T cells with CD4+CD25+ T cells. Applicant further argues that a person of ordinary skill in the art would understand that in order for the Tr1 regulatory cells to isolated, it would be necessary to separate the anergized CD4+CD25- T cells from the CD4+CD25 T cells.

"Isolated" Tr1-like regulatory T cells might merely indicate that the cells have been "isolated" from a subject, and does not necessarily indicate that the regulatory cells have been separated from the CD4+CD25+ T cells, as asserted by Applicant. The claims as filed recite a method for producing isolated Tr1-like regulatory T cells by anergizing CD4+CD25- T cells by contact with CD4+CD25+ T cells. Thus, it appears that the "isolated" Tr1-like regulatory T cells comprise a mixed population of CD4+CD25- T cells and CD4+CD25+ T cells that have been "isolated" from a subject. Neither the claims as filed, nor the instant specification disclose the step of isolating Tr1 like regulatory cells from the CD4+CD25+ T cells, as now claimed.

Applicant further argues that a person having ordinary skill in the art would read Examples 4 and 5 in the broader context of the disclosure as providing a teaching that anergized CD4+CD25- T cells are separated form CD4+CD25+ T cells.

As note above, examples 4 and 5 of the specification describe specific examples in which CFSE labeled CD4+CD25- T cells are cultured at a particular ratio with CD4+CD25+ T cells, followed by FACS sorting the CFSE labeled and unlabelled cells.

A specific example involving FACS sorting CFSE labeled cells does not provide adequate support for the instant claims which encompass any "separation" step.

5. The following are new grounds of rejection necessitated by Applicant's amendment.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9, 11, 29-30, 35, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jonuleit et al. (of record), in view of Nakamura et al., 2001.

Jonuleit et al. teach a method of producing human regulatory T cells comprising co-culturing CD4+ T cells (which inherently comprise CD4+CD25- T cells) with activated CD4+CD25+ T cells, followed by separating the regulatory CD4+ T cells from the CD4+CD25+ T cells (see page 256 and 258 in particular). Jonuleit et al. teach activating the CD4+CD25+ T cells by anti-CD3/CD28 stimulation (see page 256 and 258 in particular). Jonuleit et al. also teach that the regulatory T cells suppress proliferation of CD4 T cells (see page 258 in particular).

Jonuleit et al. do not teach activating the CD4+CD25+ T cells with plate-bound anti-CD3 or soluble CD28 antibodies.

Nakamura et al. teach that optimal stimulation of CD4+CD25+ T cells is performed by stimulating with plate-bound anti-CD3 antibody and soluble anti-CD28 antibody (see page 630-631, in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to activate the CD4+CD25+ T cells with anti-CD3 and anti-CD28 antibodies, as taught by Jonuleit et al., using plate-bound anti-CD3 and soluble anti-CD28, as taught by Nakamura et al. The ordinary artisan at the time the invention was made would have been motivated to do so, and have a reasonable expectation of success, since Nakamura et al. teach that plate-bound CD3 and soluble CD28 antibodies are optimal for simulating CD4+CD25+ T cells. Furthermore, the regulatory T cells made obvious by Jonuleit et al. and Nakamura et al. would produce IL-10, since they have been obtained by the method of the instant claims.

Applicant’s arguments filed 1/7/08 have been fully considered, but they are not persuasive.

Applicant argues that they have previously submitted a declaration attesting to the fact that Dieckmann et al. (which discloses the claimed invention) is Applicant's own invention. Applicant further states that page 252 of the Dieckmann article indicates that the article was submitted on April 22, 2002, and accepted on June 5 2002, without revision. Thus, Applicant concludes that the present inventors had possession of the present invention before the publication of Jonuleit et al. on July 13, 2002.

Applicant’s attempt to demonstrate possession of the instant invention before the publication of Jonuleit et al. is not persuasive. Demonstrating possession of the invention by Applicant prior to the effective date of a reference requires the submission of an affidavit or declaration under 37 CFR 1.131 by the inventor of the subject matter, the party qualified under 1.42, 1.43, or 1.47, or the assignee when it is not possible to produce the affidavit or declaration of the inventor (see MPEP 715.04). Attorney statements as to the invention by Applicant before the date of the reference cannot not take the place of evidence in the form of an appropriate affidavit or declaration (see MPEP 716.01c). Additionally, it is noted that contrary to Applicant’s assertion, the Dieckmann article merely states that

the article was accepted on June 5, 2002. This does not exclude the possibility that revisions might have occurred to the manuscript before publication.

7. Claims 1-2, 7-15, 37, and 39, are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A method comprising anergizing CD4+CD25- T cells by contacting with "activated" CD4+CD25+ T cells, wherein the "activated" CD4+CD25+ T cells are produced by subjecting the cells to "plate bound anti-CD3 and soluble anti-CD28 antibodies" (Claims 1 and 37 and dependent claims 11, 29-30, and 35).

Applicant indicates that support for the new limitations of the claims can be found on pages 1, 2, 8, and in Example 1. A review of the specification fails to reveal support for the new limitation.

On pages 1, 2, and 8, the specification describes the results of previous studies which demonstrate that CD4+CD25+ T cells inhibit proliferation of T cells after stimulation via their TCR. However, the instant claims are drawn to a method of producing regulatory T cells using "activated" CD4+CD25+ regulatory T cells, and not to a method of inhibiting or suppressing the proliferation of T cells using TCR stimulated CD4+CD25+ T cells, as is disclosed in the prior art. The specification in Example 1 describes a specific example of co-culturing CD4+CD25+ T cells and CD4+CD25- T cells with plate bound anti-CD3 and soluble anti-CD28 antibodies. As an initial matter, it is noted that a specific example of activation with anti-CD3 and anti-CD28 does not provide adequate support for contacting with any "activated" CD4+CD25+ T cell. However, even if the claims were limited to activation with plate-bound anti-CD3 and soluble anti-CD28, the specific example cited by Applicant does not provide adequate support for the more generic claims of the instant application. For example, the examples

involve co-culturing T cells at a 1:1 ratio, followed by separation of CFSE labeled T cells by FACS. The instant claims encompass co-culturing any ratio of cells and separating human Tr1-like regulatory T cells by any means. Furthermore, the instant claims recite that the that CD4+CD25- T cells are contacted with CD4+CD25+ T cells that have been activated by anti-CD3 and anti-CD28 antibodies. Thus, the claim does not require that the CD4+CD25- T cells be contacted with the CD3 and CD28 antibodies, as is the case in the specific example cited by Applicant.

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 6am - 2pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amy E. Juedes, Ph.D.
Patent Examiner
Technology Center 1600

/G.R. Ewoldt/
Primary Examiner, Art Unit 1644